# "Revolutionizing Drug Design and Development with In Silico Techniques"

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## Abstract:

Discovery pharmacokinetics has moved a long way from starting off as service function which served to improve basic PK parameters such as clearance, half-life and bioavailability in potency-optimised compounds in response to the excessively high attrition of 40% due to poor pharmacokinetic properties of drug candidates during clinical testing in the 1980s and early 1990s. Even in its rather service-oriented role, the impact of addressing ADME issues from early on in drug discovery programmes was astonishing, reducing PK-related failure rates down to 10% in about a decade. The impressive effect has owned discovery DMPK not only fullacceptance; it is now seen at the core of drug discovery being an integral part of every drug discovery project.Although, today, we are still a long way from understanding and translating cellular effects to pharmacodynamic and safety-related effects in tissues and further to clinical readouts, the exposure-based PK support is a powerful approach that helps advancing. the discovery, optimisation, selection and characterisation of high-quality drug candidates with PK/PD properties that carry sufficient potential to show efficacy and safety in patients at the predicted dose and dosing scheduling andthe development through ultimately allowing a more rigorous testing of new disease hypotheses in patients without bias due to uncertainty in target exposure, making clinical proof-of-concept studies much more powerful than in the past.

## Introduction

The term "in silico" refers to invivo and invitro studies carried out using modern computing applications and informatic technology as scientific tools to expand and improve our understanding. More precisely, it refers to the use of this data in the development of computational models or simulations that can be used to generate predictions, propose hypotheses, and ultimately lead to medical and therapeutic breakthroughs.Until Sieburg (1990) and Danchin et al (1990) published the word with their use in 1991, the term "in silico" was not clearly delineated in literature. Danchin (2002) presents a quotation in a more

recent work that provides a succinct and clear representation of the possibilities of computational techniques in chemistry, biology, and pharmacology. In silico pharmacology is a rapidly expanding field that encompasses the development of systems for capturing, analysing, and integrating biological and medical data from a variety of sources using software(Ekins et al 2007).

The term "pharmacokinetics"is the study of drug kinetics, entails a quantitative examination of the physiological processes of absorption, distribution, metabolism, and excretion (ADME). It also relates to how and where the pharmacological substance is dispersed throughout your body after administration, as well as how the drug is metabolised and eliminated by your body.

**Pharmacokinetics involves four processes:**

- Absorption: Transfer of medicines or chemicals into the bloodstream shortly after they are given to a patient.
- Distribution: Process of dispersing the medicine throughout the body's tissues and fluids.
- Metabolism: Irreversible conversion of drug into metabolites. First drug is metabolized by the liver to made more water-soluble before reaching the kidneys, where it is eliminated from the human body.
- Excretion: Process of removing a drug from anindividual's body.

The term "in silico ADME-PK" refers to the use of computer modelling to comprehend structure-property correlations and forecast DMPK (drug metabolism and pharmacokinetics) features from compound structure. ADME-PK stands for absorption, distribution, metabolism, excretion, and pharmacokinetics.

In silico ADME-PK focuses on providing design guidance for new compounds with enhanced ADME features. The most popular method for relating a compound's structure is the QSPR (quantitative structure property relationship) technique.

In silico ADME-PK has the potential to increase the likelihood of identifying compounds with favourable ADME features when used properly during the discovery phase.

Appropriately applied during the discovery phase, in silico ADME-PK has the potential to enhance the probability of identifying compounds with favourable ADME properties.Importantly, these in silico tools are not always intended to be in lieu of

experimental measurements, but are intricately connected with the preclinical assay they attempt to predict and are ideally applied, by chemists and DMPK scientists alike, pre-synthetically to guide the next round of synthesis. The intended result of such effort is to accelerate the drug optimization process by reducing the number of cycles of synthesis necessary to identify a quality drug candidate. Additionally in silico ADME tools can be used to prioritize in vitro testing after synthesis.

The present impact will be discussed as well as the importance of paying attention to the purpose and quality of the experimental assay being modelled and the resulting implications in model building, evaluation and use. The review further suggests individual components necessary to implement a successful in silico ADMEPK modelling culture and infrastructure in industry. Complementary discussions focusing on the technical aspects of building an ADME QSAR infrastructure can be found elsewhere.7 While the work described focuses mainly on QSPR modelling, many of the learning points are transferrable to other technologies such as molecular matched pairs and chemical data mining, which will be discussed briefly before the conclusion of the manuscript.The technologies discussed in this work require availability of hundreds of consistently measured data-points for each property target of the modelling effort; this could be a practical limitation for scientists working in small organizations approaching this field.

## Types ofdrug design

Drug discovery and development is very expensive and time-consuming process. Traditional approaches to drug discovery rely on a step-wise synthesis and screening of large number of compounds to identify a potential candidate. Over the past ten to twenty years, there is an increased effort to apply computational power to the combined chemical and biological space in order to streamline drug discovery, design, development and optimization Kapetanovic (2008).

Computational methods are expected to play an imperative role in understanding the specific molecular recognition events of the target macromolecule with candidate hits leading to the design of improved leads for the target Shaikh et al (2007).Computer Aided Drug Design (in silico) approaches have been widely employed in Lead Identification and Lead Optimization stages of drug development against various targets over the years.Advances in computational techniques and hardware have facilitated the application

of in silico methods in the discovery process. Drug Design can be categorized as two types: Structure based drug design (SBDD) and Ligand based drug design (LBDD).

There are two types of drug design; one is "ligand-based drug design" and the other is "structure-based drug design

- **Ligand based drug design (LBDD)**
- **Structure based drug design (SBDD)**

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A strategy called ligand-based drug design, which focuses on understanding of compounds that bind to the desired biological target, is employed in the lack of 3D information about the receptor. 3Dconnections between quantitative structure and activity (3D QSAR) and the most significant and often used methods are pharmacophore modelling.tools for designing ligand-based drugs.3D quantitative structure activity relationships (3D QSAR) and pharmacophore modelling are the most important and widely used tools in ligand-based drug design.

**Structure based drug design (SBDD)**

Structure based drug development (SBDD) is one of the earliest methods used in the drug designing.Important molecules in a certain metabolic or cell signalling pathway that are thought to be associatedwith particular disease state are called drug targets and they are usually key molecules in that pathway V. Srinivasa Rao and K. Srinivas (2011).Drug ingredients are intended to alter the structure and function of disease-related proteins and enzymes through inhibition, restoration, or other means Ramsay and Tipton, (2017).For the purpose of developing new therapeutic molecules, SBDD makes advantage of the 3D geometrical shape or structure of proteins which are identify through nuclear magnetic resonance (NMR) or x-ray crystallography methods.With the help of these methods, structure of Protein can be determined with resolutions as low as a few angstroms (approximately 500,000 times smaller than the diameter of a human hair) Suresh et al., (2006).At this resolution, scientists may accurately look at interactions between protein and possible therapeutic compounds,especially for the creation of novel therapeutics that stimulate or inhibit the receptor protein.

**History and evolution of in silico approaches**

Albert (1971, 1985) summarised as masterfully that drug discovery did not wait for the advent of informatics to be born and to grow as sciences. the earliest intuitions and insights in structure–activity relations can be traced to the nineteenth century. A relation between activity and a physicochemical property was firmly established by Meyer (1899) and Overton (1901), who proposed a 'Lipoid theory of cellular depression' such that the higher the partition coefficient between a lipid solvent and water, the greater the depressant action. Such papers paved the way for the recognition of lipophilicity and electronic properties as major determinants of PD and PK responses, as best illustrated by the epoch-making and still ongoing work of Corwin Hansch (Hansch and Fujita, 1964; Hansch, 1972), a founding father of drug design.

Other pioneers (for example, Crum Brown and Fraser; reviewed by (Albert, 1971)) saw that chemical structure (that is, the nature and connectivity of atoms in a molecule, in fact the two-dimensional structure (2D) of compounds) also played an essential role in pharmacological activity. The conceptual jump from 2D to three-dimensional (3D) structure owes much to the work of Cushny (1926), whose book summarises a life dedicated to relations between enantiomerism and bioactivity. This vision was expanded in the mid-twentieth century by the discovery of conformational effects on bioactivity (Burgen, 1981). In parallel with our growing understanding of the concept of molecular structure, a few visionary investigators in the late nineteenth and early twentieth centuries (for example, John Langley, Paul Ehrlich and Alfred Clark; reviewed by (Arı¨ens, 1979; Parascandola, 1980) developed the concept of receptors, namely the targets of drug action. The analogies between receptors and enzymes were outlined by Albert (1971).

## Pharmacokinetics in drug discovery

### Target identification

The first step in target-based drug development is the identification of a possible therapeutic drug targets and comprehension of its function in the disease process.Typically, a target is a single molecule, like a gene or protein, involved in a signalling pathway that is unique to the infectiousness or persistence of a microbial pathogen, is referred to as a drug target.Some approaches attempt to restrict the functioning of the pathway in the diseased state by forcing an essential molecule to stop functioning. Drugs may be designed that bind to the active region and inhibit this key molecule.Another strategy would be to strengthen the metabolic pathway by utilizing appropriate molecules in the pathways that might have been influenced by the diseased condition (Taylor and Francis, 2006).Bioinformatics,

chemoinformatic, and data mining strategies including homology-based, ligand-based, structure-based, high throughput screening (HTS), text mining, microarray technologies, pattern matching, etc. are used to pinpoint the precise target and the particular patient group.

**Target validation**

A thorough assessment must be conducted after a pharmacological target has been discovered to show that modulating the target will have the desired therapeutic impact.Target validation is the primary limitation in the drug discovery process. The target validation step will go much faster if this procedure can be sped up with computational tools.Finding out whether changing a target's function would result in the desired clinical outcome, specifically the amelioration or eradication of a phenotype, is a step in the target-validation process.It is possible to carry out in silico characterization accomplish a variety of techniques including genetic network mapping, protein-pathway mapping, protein-protein interactions, disease locus mapping, and predictions of subcellular localization.The initial choice of a target may be based on preliminary findings linking a disease or health condition to a particular cell type, protein expression, possible binding sites, cross-organism confirmation, or pathways implicated in an illness or health condition (Bleicher et al., 2003).

**lead identification**

Modern drug discovery revolves around the identification of small molecule regulators of protein activity and the method of developing these into high content lead series (Robert AG 2006).Hits can be discovered using one or more technological methods, such as high-throughput biochemical and cellular assays, natural product assays, structure-based design, peptides and peptidomimetics, chemo genomics and virtual HTS, as well as innovations based on published works and patents (Suresh et al., 2006).It is helpful to take into account the numerous approaches that have been described for hit and lead identification, assay creation, where the target is converted to an HTS assay system, and drug discovery techniques in order to design effective methods.

**Lead optimization**

Lead optimization is a difficult, non-linear technique that aims to produce a drug canditate by modifying the chemical structure of a verified hit to enhance its pharmacological properties. Target affinity and selectivity are tuned for lead structures.Currently, docking methods are used to support structure-based absorption, distribution, metabolism, and excretion (ADME).To give experimental proof of concept, drug candidates generated using this method

must be verified on an animal model of a particular disease.This fundamental transition in the drug discovery process from a physiology-based approach to a target-based approach offers high screening capacity and promotes the formulation of straightforward, explicit requirements for candidate medications, enabling the implementation of rational drug design (Klaus et al., 2001)

**Pre-clinical testing**

When a novel active chemical is to be utilised as a pharmaceutical product in humans, risk is minimised through preclinical investigations and testing methodologies, both with and without the use of animal testing techniques.The shift from preclinical to clinical trials in the development of pharmaceutical goods should be as quick, risk-free, simple, and affordable as feasible (Glossary of Clinical Trial Terms, NIH Clinicaltrials.gov).Tests are conducted in vivo and in vitro by scientists. Vitro, which means "glass" in Latin, refers to laboratory investigations done in test tubes and beakers, whereas vivo, which means "life," refers to research done on living cell cultures and animals. Pharmacology, toxicology, preformulation, formulation analysis, and pharmacokinetics are all part of preclinical testing.

**Clinical testing**

A clinical trial, also known as clinical research, is a research study conducted on human participants to address certain health-related problems. The quickest and safest approach to identify therapies that benefit patients and strategies to enhance health is through well designed clinical trials.The investigators' tasks during the clinical trial include selecting participants who fit the stated criteria, giving the treatment(s), and gathering information on the participants' health over a predetermined time frame. The U.S. National Institutes of Health (NIH) categorises trials into five main types: extended access, compassionate use, screening, diagnostic, therapeutic, and quality of life trials (Glossary of Clinical Trial Terms, NIH Clinicaltrials.gov).

**NDA and FDA approval**

In order to formally request that the Food and Drug Administration (FDA) authorise a new pharmaceutical for sale and marketing, drug sponsors must submit a new drug application (NDA) to the FDA.The NDA's objectives are to offer sufficient details for FDA reviewers. All of the data from earlier research years is included in the NDA, along with recommendations for the production and labelling of the novel drug.Experts from the FDA

review all the data in the NDA to decide whether it supports the drug's safety and efficacy as required for approval.

**Significance of in-silico drug discovery process**

There is a growing need for computational tools that can locate and analyse active sites and suggest possible therapeutic compounds that can selectively bind to these sites. These tools are now available through crystallography, NMR, and bioinformatics methods.The amount of time and money needed to design a new medicine is excessive and intolerable. An estimated $880 million and 14 years of research are required to develop a new medicine before it can be sold on the market. It is essential for computers to be involved at some conceivable stages of the drug discovery process in order to reduce the expense and time needed.

**Bioinformatics in computer-aided drug design**

Bioinformatics is an interdisciplinary field that uses computer techniques to tackle biological issues in the field of life science.A specialised field called computer-aided drug design (CADD) simulates drug-receptor interactions using computational techniques, which needed in a number of key areas of bioinformatics and these technologies are based on biological information, bioinformatics software, and instruments.

**Homology modeling**

Building an atomic-resolution model of the "target" protein from its amino acid sequence and an experimental three-dimensional structure of a comparable homologous protein is known as homology modelling, also known as comparative modelling of proteins (the "template").Proteins are the most common therapeutic targets, therefore understanding their three-dimensional structure is crucial. The human body is thought to have between 500,000 and 1 million proteins.In order to produce an alignment that maps the residues in the query sequence to the residues in the template sequence, homology modelling must first identify one or more known protein structures that are likely to resemble the structure of the query sequence.However, sequences with less than 20% sequence identity can have highly diverse structures (http://en.wikipedia.org/wiki/Homology modeling). It has been demonstrated that protein structures are more conserved among homologues than protein sequences.The Swiss-Model Repository is a database of protein structures produced using the popular homology modelling application “Modeller” (Richard, 2006).

**Interaction networks**

Finding the right fit between a receptor and a possible ligand is done through the process of docking. According to http://mndoci.com/2007/02/10/evaluating-protein-ligand-interactions/, docking actually consists of two independent components: "docking," which is the search strategy to find acceptable conformations or poses, and "scoring," which is a gauge of the affinity of various poses.An interaction network is a collection of nodes joined together by features. According to Wikipedia, if a feature is both physical and molecular, the interaction network is made up of the molecular interactions that are often present in cells.A method of molecular modelling is called protein ligand docking. Predicting the location and orientation of a ligand (a small molecule) when it is bound to a protein receptor or enzyme is the objective of protein-ligand docking.

**Microarray analysis**

The new technology known as DNA technology or microarray analysis promises to improve biotechnology even further. Simple organised collections of DNA molecules with a known sequence make up microarrays. They can have a few hundred to hundreds of thousands of sets and are typically rectangular.At a certain location on the substrate, each individual feature is placed on the array. The DNA molecule fixed to each characteristic never changes in identity. This fact is used by scientists to compute the outcomes of their experiments.Scientists can simultaneously identify and examine the expression of thousands of genes in a tiny sample using microarray analysis.It thus promises to make it possible for biotechnology and pharmaceutical firms to identify potential drug targets. Microarray analysis can help pharma companies choose the most suitable participants for clinical trials of novel medications by assisting in the identification of individuals with comparable biological patterns.Future advances in medical science may make it easier for doctors to choose treatments for specific patients that are most successful or have the fewest negative effects.It has potential uses in a number of areas, including studies of transgenic animals, tissue microarrays for cancer and other disorders, and normal tissues and cells during development.The development of new medications may benefit from the use of microarray technology. According to Jeffrey Williams, CEO of Genomic Solutions, based in Ann Arbor, Michigan (http://www.sciencemag.org/site/products/micro.xhtml), "It has been amply established that the technique can identify genes that have been upregulated or downregulated."By utilising text mining, association rule mining, and machine learning techniques, DruTiMine (drug target integrative miner), an IBM research project carried out

at IBM Centre of Advanced Studies in Cairo (Cairo-CAS), aims to identify drug targets for a specific disease, including genes, proteins, and chemical compounds (Hisham,2006).

## Conclusion

In this endeavour, scientists from various large pharmaceutical companies who have extensive experience in the in silico ADME-PK field will pool their knowledge.Although in silico ADME-PK has been a reality in industry since Lipinski's Rule of 5 was introduced, it is frequently seen as an extension of other fields like computational chemistry or drug design and development.Because of this, scientists working in this field typically have backgrounds in computer science, chemistry, or DMPK science and lack formal training in in silico ADME-PK.On the one hand, this has encouraged an open environment, giving people with various specialties (such as in vitro, in silico, statistics, analytical, PK, structural biology, synthetic chemistry, machine learning, etc.) a chance to work together and create.However, unlike the more mature PBPK and structure-based design fields, in silico ADME-PK is just now starting to turn the experience and knowledge gathered over the years into best practises, shifting the focus from creating technologies to using them, and changing the goal from demonstrating potential to demonstrating impact.The use of well-integrated platforms of models in the screening cascades to enhance the optimization flow for the desired attributes has tremendously benefitted a number of businesses.

Drug development is a dynamic process; at the moment, regulatory organisations are encouraging and rewarding emerging breakthrough cures, which opens up uncharted biological and chemical territory.Companies that can quickly translate first HTS screening hits into drug-like molecules suitable for investigating the efficacy and safety of novel targets may succeed in this environment. QSPR models, MMP, and other chemical data mining techniques work best in this area.Since the process of discovering and developing new drugs is time-consuming and expensive, it will be crucial for in silico ADME researchers to gather industry best practises in this field and increase the number of adopters.It begins with target identification, follows with target validation, and then names medication candidates. Any brand-new medicine must pass rigorous preclinical and clinical testing and receive FDA approval before it can be sold.Because experimental procedures are limited in throughput, accuracy, and expense, drug development has recently switched to in silico methods including homology modelling, protein-ligand interactions, microarray analysis, vHTS, and others.The development of quick and precise

target identification and prediction methods for the discovery relied heavily on in silico approaches.

## Summary

### Abbreviations Used

ADME-PK, absorption, distribution, metabolism, excretion, and pharmacokinetics; AZ, AstraZeneca; Caco-2, human colon carcinoma cell line; CLint, Intrinsic clearance; CLint,u, unbound intrinsic clearance; GNE, Genentech; h-fup , fraction unbound in human plasma; HLM, human liver microsomes; HT, high throughput; IQ, International Consortium for Innovation through Quality in Pharmaceutical Development; IT, information technology; JAK-1, Janus kinase 1; MDCK, MadinDarby Canine Kidney epithelial cells; MDR1, Multi drug resistance gene 1, coding Pgp; MMP, matched molecular pair; MMS, matched molecular series; MPO, multiparameter optimization; PBPK, physiologically-based pharmacokinetics; Perm, permeability; PK/PD, pharmacokinetic-pharmacodynamic; Rat_Mic_Clint,u, unbound intrinsic clearance in rat liver microsomes; RMSE, Root mean squared error; RMSEP, root mean squared error of the prediction; StDev, standard deviation; TDI, time-dependant inhibition; Vss, volume of distribution at steady state.

### Acknowledgements

Pratibha Yadav gratefully acknowledges Dr Shri Devedi (Principal, Mata Jijabai Govt. PG Girls, College) for his insightful efforts in tabulating the successful applications of in silico approaches which was inspirational.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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